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EP00/976

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09/913781

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(21) *Patentansökningsnummer* *9900530-8*
Patent application number

(86) *Ingivningsdatum* *1999-02-15*
Date of filing

Stockholm, 1999-12-22

För Patent- och registreringsverket
For the Patent- and Registration Office

Emma Johnsson

Avgift
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Title

A device for concentrating and/or purifying macromolecules in a solution and a method for manufacturing such a device.

Technical field

This invention relates to a device for concentrating and/or purifying macromolecules in a solution and a method for manufacturing such a device. The device comprises a compartment for the sample to be processed and a compartment for the filtrate separated by means of at least one membrane. More specifically the invention concerns a new way of fixing the membrane in pressure resistant sealing relation in the interface between said two compartments. Devices manufactured according to the invention may be used in centrifuges, as tangential flow modules, as gas pressurised cells or with hand operated syringes, etc..

Background art

Many biotechnology laboratories and health care institutions use micro- and ultrafiltration methods for the processing of biological solutions. As examples, filtration is used as a sterilising step to remove bacteria, as a clarification step to remove suspended solids and contaminants, as a concentration step for proteins and other macromolecules or as a purification step to eliminate unwanted micro-molecules such as salts. Alternative filtration methods, devices and membrane cut-offs are used to suit specific applications and process requirements.

Centrifugal forces, gas or liquid pressure or vacuum are typically used to provide the vector to push or pull solvent and small micro-molecules through the membrane whilst solute components larger than the cut-off of the membrane are retained. In most applications, the higher the pressure or vacuum exerted, the higher the filtration speed relative to the membrane area used. Generally, high speed small area devices are preferred.

Typical devices of the type here referred to include a compartment for the sample to be processed and a compartment for the filtrate. These compartments are communicating through at least one common aperture in which a porous membrane such as a micro-porous, ultrafiltration or reverse osmosis membrane is arranged. The membrane is sealed at its periphery to the aperture either to the peripheral surface of the concentration or filtrate compartment or both

The membrane is usually supported on the permeate side to withstand the pressure. There is an inlet provided for introducing a liquid sample in the concentration compartment and an outlet for the filtrate from the filtrate compartment. In so called tangential flow devices there is an additional outlet arranged in the concentration compartment to allow sample circulation.

It is clear that the sealing of the membrane must meet very high requirements so that the liquid to be processed will be prevented from by-passing the membrane. The membrane may be sealed in a variety of ways such as by means of heat sealing, adhesive or solvent bonding, ultrasonic welding or by interference fit.

Material and wall thickness for the compartments which are also sealed together are chosen in order to withstand the operating pressure.

Devices are sometimes additionally provided with separate pressure holders or membrane assemblies are placed between external pressure plates which are typically bolted together to provide additional support.

One of the problems with the prior art devices is the difficulty in obtaining a satisfactory compromise between seal reliability both for the membrane and/or for the joint between the compartments, adequate pressure containment and low manufacturing cost.

For practicality and cost reasons , it is desirable to mould filtration devices but it is not always possible to mould membrane support sections of sufficient thickness to withstand high operating pressures because it is difficult to mix thick and thin areas when moulding. The alternative of using separate pressure holders or external pressure plates is both expensive and inconvenient for small devices. Also, depending on the membrane and component materials used, suitable sealing systems are frequently expensive and/or unreliable when used at high pressure.

Another problem is achieving a sufficiently strong seal between the compartments, particularly with incompatible or non sealing materials and in large area devices that must withstand higher overall pressures.

The centrifugal filtration device as described in US-A-5647990, the teachings of which document are incorporated herein, has a disadvantage in the potential for damaging the relatively fragile membrane when the retentive sleeve is pushed onto the concentration chamber as frictional forces tend to also push the membrane out of its required position.

Pressure containment and seal integrity is also limited by the difficulty in moulding a sufficiently thick membrane supporting plate and the incomplete support provided to the sealing area of the membrane due to filtrate outlet passages that directly cross the seal area in this prior art device. The problem of frictional forces and incomplete seal support is further accentuated when the membrane is not first sealed to the concentration compartment but sealing and

assembly is effected in a single operation by the compression during assembly of the perimeter of the membrane to the aperture of the said compartment.

The document GB-A-9819686.8 is showing a so called tangential flow device. The economy of this device is limited by the need to machine the pieces of the device due to the difficulty of moulding the components with a sufficient thickness to contain high pressure. Additionally relatively high cost bolting mechanisms are required to hold the assembled device together in a pressure resistant way.

Brief description of the invention

One object of the present invention is to provide a device of the type mentioned above which is simple to manufacture whilst providing increased overall reliability.

A further object is to provide a method according to which the membrane will be sealed to the device during the assembly in a single operation.

A further object is to provide a device for which it is possible to choose materials for the concentration and filtrate compartments which do not require heat, or ultrasonic seal compatibility to each other and/or to the membrane used.

A further object is to provide a device which has a supported seal around the whole periphery of the membrane.

A still further object of the invention is to provide a device which is possible to re-open and re-close e.g. after processing in order to inspect and/or replace the

membrane without damaging the concentrating and filtrate compartments or the membrane. This feature of course offers a high degree of flexibility.

The problems of the prior art are overcome by the provision of the device and the method for manufacturing said device as defined in the appended claims.

Brief description of the figures

Other objects, uses and advantages of this invention will be apparent from the reading of this description which proceeds with reference to the accompanying drawings forming part thereof and wherein:

Figure 1 shows in perspective a device according to the present invention implemented as a tangential flow module.
Figure 2 shows in section the insert according to figure 1.
Figure 3 shows a side view of the embodiment according to figure 1.
Figure 4 shows a top view of the embodiment according to figure 1 as assembled.
Figure 5 shows in section the assembled device according to figure 4.
Figure 6 shows a top view of the upper transparent part of the insert according to figure 1.
Figure 7 shows a top view of the lower transparent part of the insert according to figure 1.
Figure 8 shows a top view of the upper transparent part of another embodiment of the insert according to figure 1.
Figure 9 shows in perspective another embodiment of the device according to the invention implemented as a centrifugal filtration device.
Figure 10 illustrates the assembly of the device according to figure 9.
Figure 11 shows an assembled device according to figure 9.

Figure 12a shows in section an assembled device according to figure 9.
Figure 12b shows in section an assembled device according to figure 9 provided with a variant of the sleeve.
Figure 13a and b show two horizontal sections through the assembled device according to figure 12a.

Detailed description of the invention

Figure 1 shows in perspective a device according to the present invention implemented as a tangential flow filtration module or cell which can be used e.g. for concentrating and or fractionating macromolecules in a solution. In a filtration system this type of filtration module is connected to a pump that typically draws liquid from a sample reservoir through the module or cell and recirculates sample liquid through a loop including the cell. The module is connected in this loop by means of an inlet 3 and an outlet 4 for sample liquid. This inlet and outlet are according to the invention arranged on an insert 1. The necessary system pressure is created by a flow restrictor positioned at the outlet 4 of the cell.

The insert 1 comprises a concentration compartment and a filtrate compartment separated by a membrane. Figure 6 shows an example of a concentration compartment 10 in the form of a thin channel for the sample liquid arranged in the upper part 12 of the insert, cf. figure 2, having an inlet 3 and an outlet 4 arranged at its end portions. This compartment is separated from the co-operating filtrate compartment 11 arranged in the lower part 6 of the insert 1 by means of a membrane. An example of such a filtrate compartment is shown in figure 7.

Due to the pressure difference between the feed side and the permeate side of the membrane filtrate is permeating through the membrane into the filtrate compartment and is taken out via the outlet 5 for collection outside the cell.

Figure 2 shows in section an example of an insert according to figure 1. The lower part 6 has a generally flat upper surface 16 which will be used as a membrane support. This surface is provided with a multitude of parallel grooves forming channels 9 for the filtrate, cf. also figure 7. These channels are all communicating e.g. by means of a transversal outlet channel 14, cf. figure 5, connecting the end portions of the channels 9 on one side of the insert in order to feed all the collected filtrate to an outlet 5 for the filtrate from the cell.

The membrane 15, cf. figure 5, is positioned on top of the surface 16 reaching all the way to the vertical wall portions 13 along the edge of the said surface. Along the inner side of said vertical wall portions on said surface 16 a generally flat gasket seat 8, cf. figures 2, 5, 7, is arranged in this embodiment. This means that the membrane all around its periphery will have a generally flat support. A gasket 7, in the form of an O-ring, in this embodiment, is arranged on top of the membrane over the gasket seat and the upper part 12 is closing the insert.

A sleeve 2, 2', preferably manufactured by moulding a suitable plastic material is surrounding the insert. In the embodiment shown in the figures 1, 3, 4, 5 the sleeve is implemented in two parts 2 and 2' which at the assembly are pushed over the insert from two opposite sides to form the complete sleeve. At the assembly this sleeve is compressing the insert 1 without frictional forces on the membrane thereby simultaneously creating, in one step, the concentration chamber and the filtrate chamber by sealing the edge of the membrane.

Thus, by just putting together a certain number of separate components without the use of any tools or adhesives it is possible to realise a filtration module which heretofore has required adhesives, bolted pressure plates, assembly tools etc..

Additionally this module is easy to take apart for inspection, change of membrane, cleaning or for any other purpose without damaging any of the constituent parts.

Figure 3 shows a side view of the embodiment according to figure 1. The introduction of the insert in the two sleeve parts is to start with very easy due to the tapered form of the sleeve and insert, cf. figure 5. Greater force is only needed at the end of the assembly during the compression of the gasket. It would also be possible to use a shrink technique to get the sleeve in place.

Figure 4 shows a top view of the embodiment according to figure 1 as assembled. At the lower part of the sleeve a dovetail rim 17 is arranged in this embodiment which could co-operate with a corresponding slot at the upper part of an adjacent module, not shown. In this way filtration cells could be stacked on top of each other if desired.

Figure 5 shows in section the assembled device according to figure 4. As can be seen the inside of the moulded sleeve has been made tapered. This is of cours practical for manufacturing purposes but also creates one possibility to achieve the necessary compressing forces for the insert 1 when this has also a tapered form. In order to achieve practically the same compressing effect but lower friction between the sleeve and the insert at the assembly the top and bottom surfaces of the insert could be made parallel and the tapered form could be realised by means of longitudinal tapered rims on the top and bottom surfaces or at least one of them. Such a solution has been illustrated in figure 8 showing tapered rims 18.

An additional advantage with the moulded sleeve in two parts 2, 2' according to the above is that a standardised thread 18 for the inlet 3 and outlet 4 for the liquid sample could easily be created during the moulding.

Many variants of the inventive idea exist. It could for example be advantageous in certain embodiments to arrange the gasket between the membrane and the filtrate compartment instead.

It is clear that a great flexibility concerning the choice of material for the different components of the filtration module has been achieved. Bonding compatibility is not necessary between any of the components in this embodiment. This means e.g. that a relative soft and flexible material could be used for the insert or part of the insert whilst a relatively rigid and strong material could be used for the sleeve. In this way the gasket could even be integrated in the upper and/or lower part 6, 12 of the insert. The gasket could thus have the form of a rim or ridge at the periphery of the upper and/or lower part in the same material as the rest of the part 6, 12.

The chemical properties of the different components could also be chosen with greater flexibility. A material with higher solvent resistance could e.g. be chosen for the internal structure in contact with the liquid flow path.

The two sleeve parts 2, 2' have been shown with closed end portions. This design gives a very strong and rigid sleeve which is able to stand high pressures. But it should be understood that these end portions are not absolute necessary in all applications.

Figure 9 shows in perspective another embodiment of the device according to the invention implemented as a centrifugal filtration device. Components corresponding to components described in connection to the embodiments according to figures 1 to 8 have been given the same designations. Thus, a

concentration compartment 12 is provided for receiving the sample to b processed. In this case the sample is not recirculated in that chamber and therefore no outlet for the sample is provided from this compartment, only an inlet 3. A gasket 7 is provided to be arranged in a groove 19 around an aperture in the wall of said compartment. A suitable piece of membrane 15 is positioned over said aperture. In the same way as before a filtrate compartment provided with a membrane support and a multitude of vertical parallel grooves forming channels 9 for the filtrate will be created by means of the component 6 when fixed against the membrane 15.

Figure 10 shows the assembled components 12, 7, 15 and 6 of the device according to figure 9. A one piece sleeve 2 will in this embodiment be pushed over said assembled components. Due to the tapered or conical form of th component 6, i.e. the filtrate compartment, and the corresponding inner form of the sleeve the filtrate compartment will be forced against the membrane 15 and will compress the gasket means against the concentration compartment. It should be noted that the membrane will only be exposed to forces perpendicular to its surface when the sleeve is positioned.

In this way a pressure sufficiently high to seal the membrane liquid tight against the concentration compartment is created and will be maintained during the centrifugal process.

Figure 11 shows the assembled device with the sleeve in position.

Figure 12a shows in section an assembled device according to figure 9. At the upper part of the filtration compartment a channel 20 is communicating to the outside. This channel can evacuate air from the filtrate channels 9 at the start of the filtration process. In this embodiment three channels 5 are provided for the outlet of the filtrate to be collected in a filtrate tube, not shown, in which the

device is partly inserted during the process. The channels 5 are at the inside communicating with a transversal outlet channel 14 as in the embodiment shown in figure 5, connecting the end portions of the channels 9 on one side of the filtrate compartment in order to feed all the collected filtrate to the outlet channels 5.

The device is resting with a flange 21 on the sleeve 2 against the edge of the filtrate tube which means that the centrifugal forces acting on the device during the process will firmly keep the sleeve in position with the flange 21 against the flange 22 on the compartment 12.

Figure 12b shows in section an assembled device according to figure 9 provided with a variant of the sleeve. In order to ensure the sealing between the gasket means 7 and the membrane at the lower part of the device the sleeve has been made less flexible in this area by the addition of a stabilising ring 23 of material around the opening in its lower part. The ring 23 can alternatively have a more flat configuration than the one shown in section in figure 12b.

As the vertical filtrate channels 9 are not reaching below the transversal outlet channel 14 in this and the other embodiments it is possible to arrange a generally flat support for the permeate side of the membrane 15 along its periphery which will ensure a regular sealing effect all around.

Figure 13a shows a horizontal section through the assembled device according to figure 12a at the upper part and figure 13b at the lower part. The tapered form of the component 6 forming the filtrate compartment is clearly illustrated.

It is clear that many variants of the basic inventive idea could be imagined. To start with devices according to the invention could be especially designed for us in a centrifuge, like the embodiment described with reference to figures 9 to 13.

But gas or liquid pressure or vacuum could also be used to provide the vector to push or pull solvent and small micro-molecules through the membrane. The first embodiment according to the above uses e.g. liquid pressure.

The gasket means could have the form of an O-ring preferably positioned in a suitable groove around one of the two apertures. Two O-rings could also be envisaged, one around each aperture. As already mentioned with reference the first embodiment above the sealing of the membrane could be achieved by means of gasket means integrated in one or both of the compartments. This embodiment is advantageous when a softer material has been used for the compartments or part thereof. In general, the flexibility concerning the choice of material for the different components (mechanical properties, chemical properties etc.) which has been discussed with reference to the first embodim nt above exists for all embodiment.

A method for manufacturing the device according to the invention would have the following steps: gasket means are first arranged around at least one of said apertures on the concentration compartment or the filtrate compartment. One of said apertures is then covered with a membrane with its feed side against said concentration compartment and its permeate side against said filtrate compartment. Said compartments are then assembled with the apertures arranged over each other and a pressure resistant sleeve is finally arranged on the outside and around the combination of said concentration compartment, said gasket means, said membrane and said filtrate compartment. Said sleeve will create and maintain a pressure sufficiently high to seal the membrane liquid tight against at least one of said compartments during the process whilst also increasing the structural support of the whole assembly.

Claims

1. Device for concentrating and/or purifying macromolecules in a solution by means of filtration through a membrane comprising a concentration compartment for a liquid sample to be processed provided with a first aperture, a filtrate compartment provided with a second aperture to be arranged over said first aperture, a membrane arranged liquid tight along its periphery over one of said first and second apertures separating said two compartments **characterised in that** gasket means are arranged around at least one of said apertures in contact with at least one side of said membrane and that said filtrate compartment on the side facing the membrane is provided with membrane support means supporting the permeate side of said membrane and that a pressure resistant sleeve is arranged on the outside and around the combination of said concentration compartment, said gasket means, said membrane and said filtrate compartment, thereby completing the assembly and creating and maintaining during the process compressing forces sufficiently high to seal the membrane liquid tight against at least one of said compartments whilst also increasing the structural support of the whole assembly.

2. Device according to claim 1, **characterised in that** said gasket means is a ring formed elastic device of O-ring type.

3. Device according to claim 1, **characterised in that** said gasket means has the form of a ridge of elastic material and is forming an integral part of at least one of said compartments.

4. Device according to any of the claims 1 to 3, **characterised in that** said sleeve is ring formed and has a tapered or conical inner surface and that at least

one of said compartments has a tapered or conical outer surface which at the assembly co-operates to create said compressing forces.

5. A method for manufacturing a device for concentrating and/or purifying macromolecules in a solution by means of filtration through a membrane which device comprises a concentration compartment for a liquid sample to be processed provided with a first aperture, a filtrate compartment provided with a second aperture, a membrane arranged liquid tight along its periphery over one of said first and second apertures separating said two compartments **characterised in that** it comprises the following steps: gasket means are arranged around at least one of said apertures, one of said apertures is covered with a membrane with its feed side against said concentration compartment and its permeate side against said filtrate compartment, said compartments are assembled with said first aperture arranged over said second aperture and a pressure resistant sleeve is arranged on the outside and around the combination of said concentration compartment, said gasket means, said membrane and said filtrate compartment, thereby completing the assembly and creating and maintaining during the process compressing forces sufficiently high to seal th membrane liquid tight against at least one of said compartments whilst also increasing the structural support of the whole assembly .

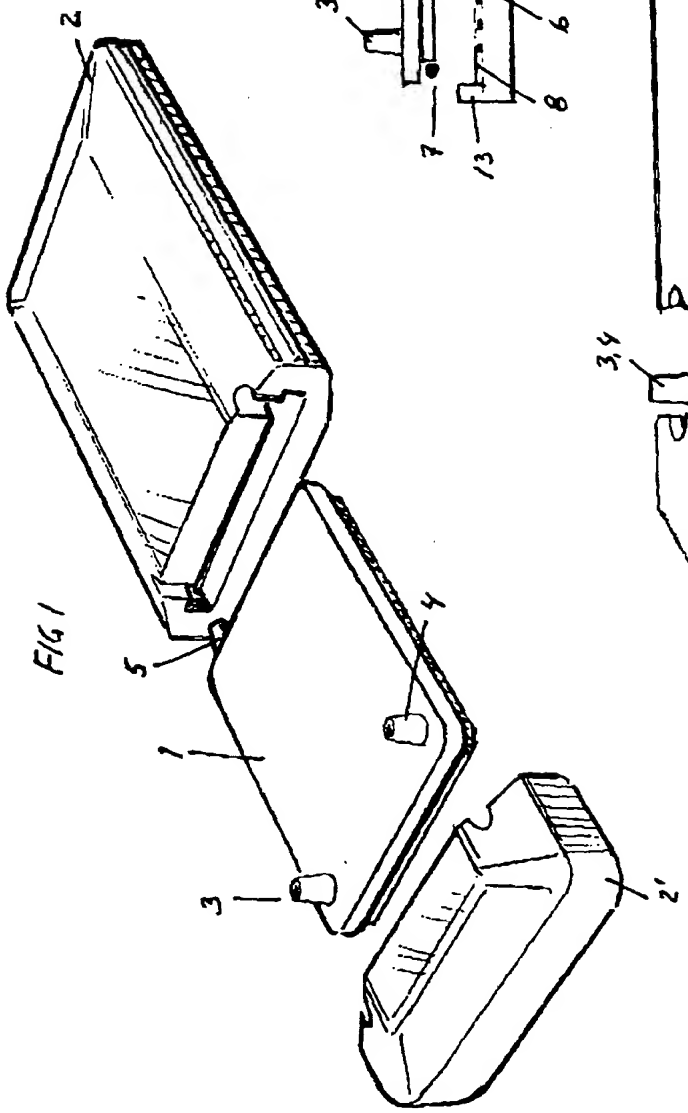

FIG 1

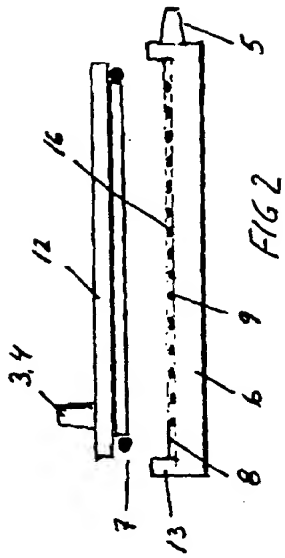

FIG 2

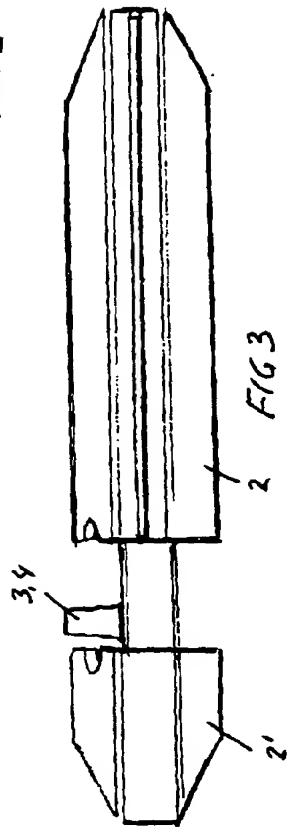

FIG 3

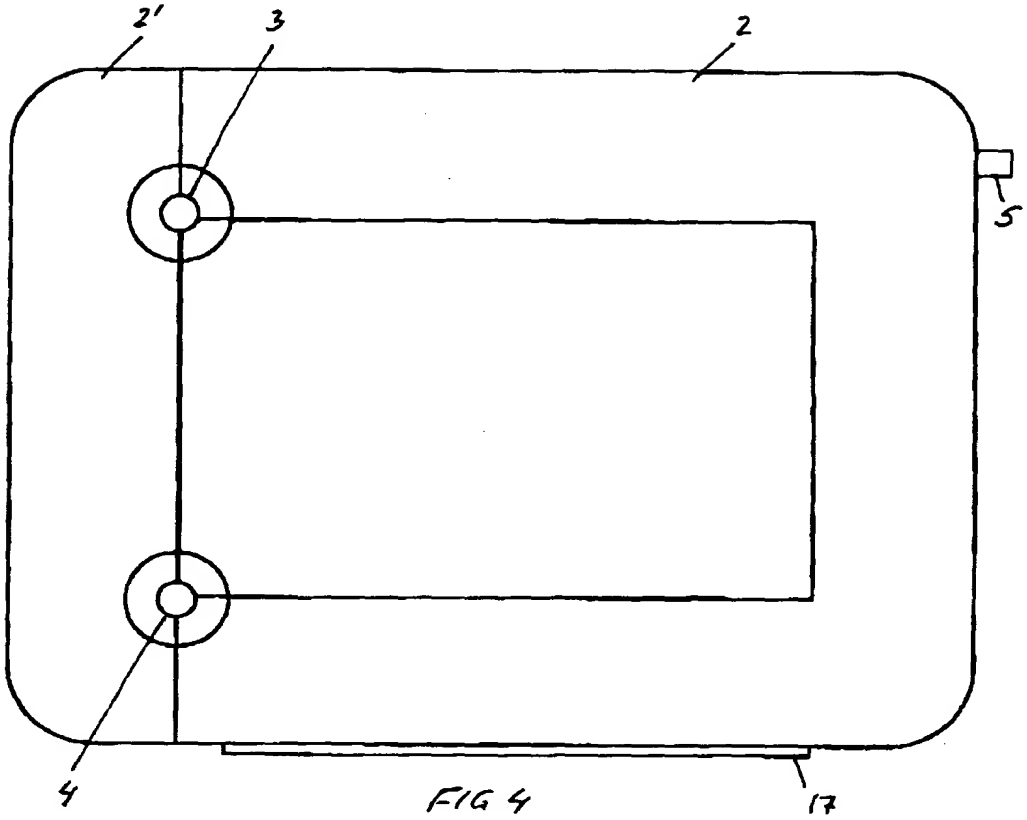

FIG 4

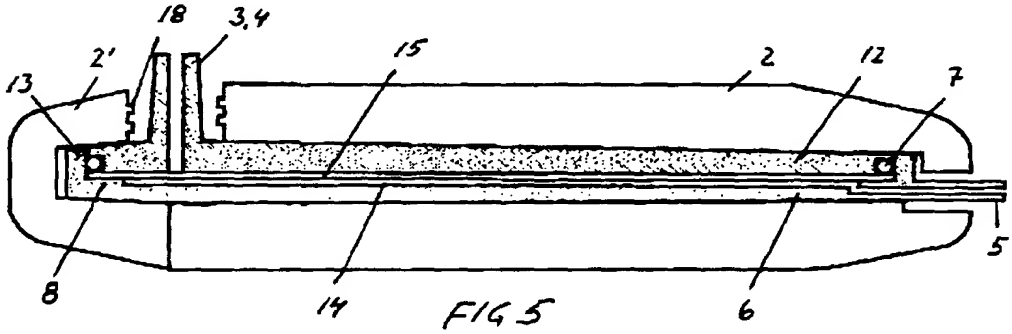

FIG 5

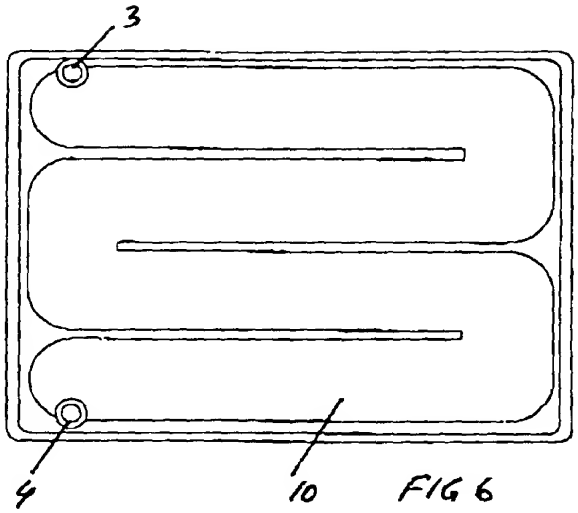

FIG 6

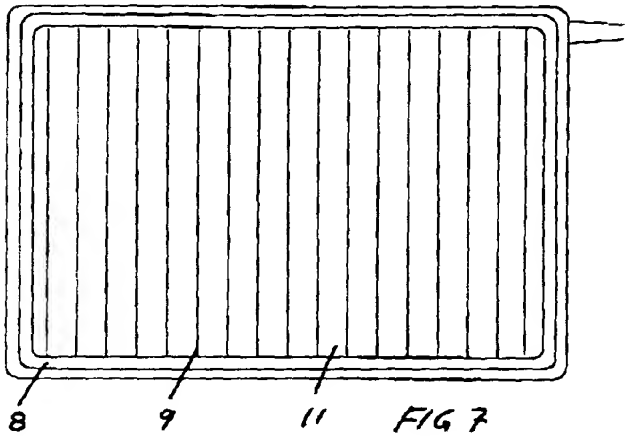

FIG 7

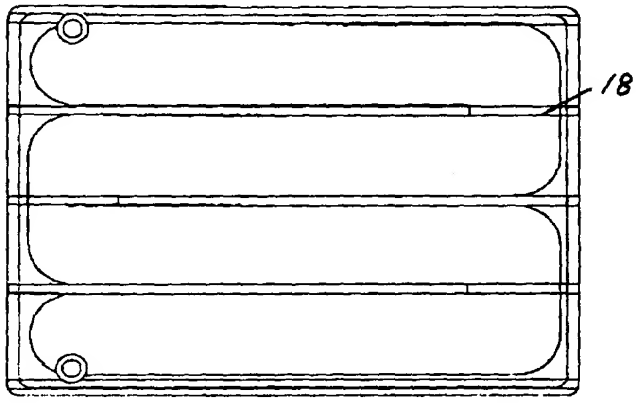

FIG 8

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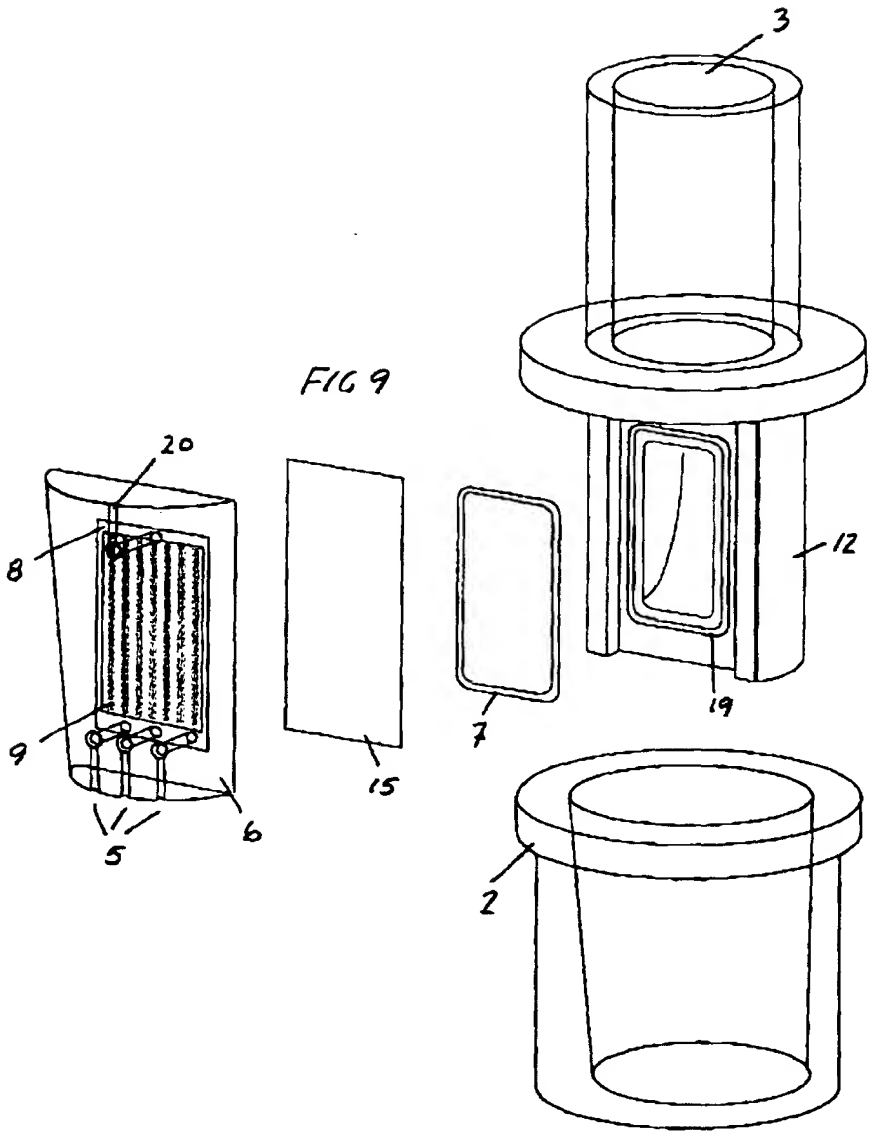
FIG 9



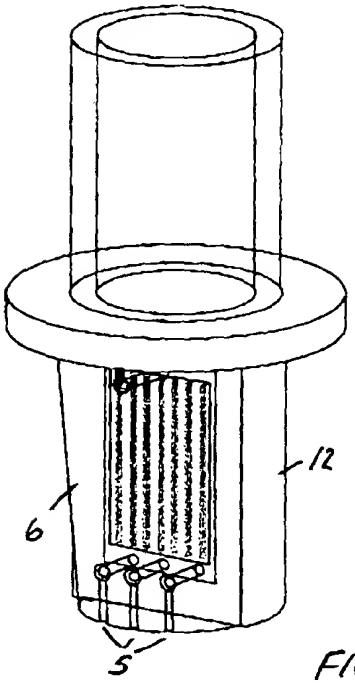


FIG 10

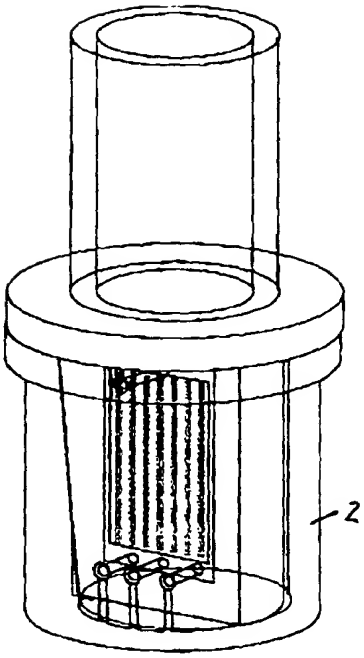
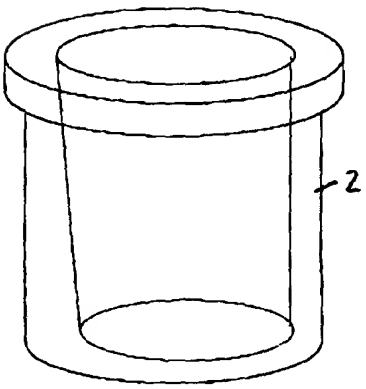


FIG 11



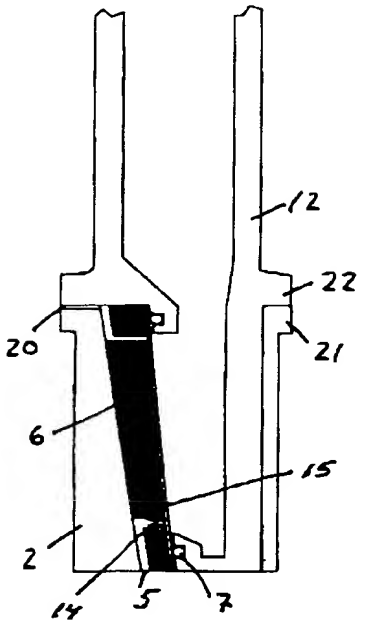


FIG 12a

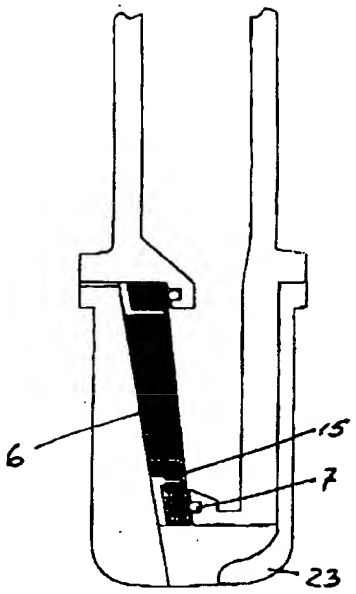


FIG 12b

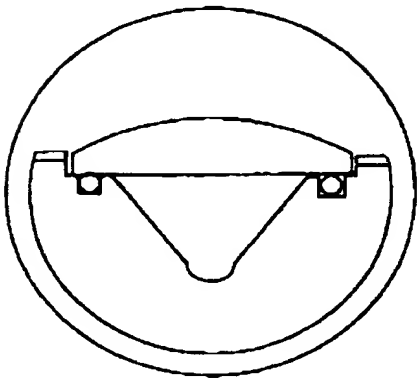


FIG 13b

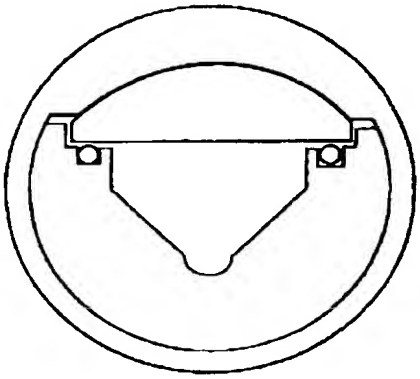


FIG 13a